Early Esophageal Cancer

Pattern of Lymphatic Spread and Prognostic Factors for Long-Term Survival After Surgical Resection

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Objective: The objective of this study was to assess the prevalence and pattern of lymphatic spread in patients with early squamous cell and adenocarcinoma and identify prognostic factors for long-term survival after resection and lymphadenectomy.

Summary Background Data: Limited endoscopic approaches without lymphadenectomy are increasingly applied in patients with early esophageal cancer.

Material and Methods: A total of 290 patients with early esophageal cancer (157 adenocarcinoma, 133 squamous cell cancer) had surgical resection with systematic lymphadenectomy. Specimens were assessed for prevalence and pattern of lymphatic spread. Prognostic factors were determined by multivariate analysis.

Results: None of the 70 patients with adenocarcinoma limited to the mucosa had lymphatic spread, as compared with 2 of 26 with mucosal squamous cell cancer. Lymphatic spread was more common in patients with submucosal squamous cell cancer as compared with submucosal adenocarcinoma (36.4% versus 20.7%). Although lymph node metastases were usually limited to locoregional lymph node stations in early adenocarcinoma, distant lymphatic spread was frequent in early squamous cell cancer. On multivariate analysis, only histologic tumor type and the presence of lymph node metastases were independent predictors of long-term survival. Five-year survival rate was 83.4% for early adenocarcinoma versus 62.9% for early squamous cell cancer and 48.2% versus 79.5% for patients with/without lymphatic spread.

Discussion: Prevalence and pattern of lymphatic spread as well as long-term prognosis differ markedly between early esophageal squamous cell and adenocarcinoma. Limited resection techniques and individualized lymphadenectomy strategies appear applicable in patients with early adenocarcinoma.

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In the Western world, adenocarcinoma has replaced squamous cell cancer as the predominant tumor entity in the esophagus. From 1975 to 2001, the incidence of esophageal adenocarcinoma rose approximately 6-fold from 4 to 23 cases per million in the United States, whereas the incidence of squamous cell cancer showed a mild decline during this time period.[1] A recent analysis has shown that this rise in the incidence of esophageal adenocarcinoma represents a real increase in disease burden and is not the result of overdiagnosis or reclassification of adjacent gastric and cardia adenocarcinoma or squamous cell carcinoma.[2]

In contrast to squamous cell cancer, specific predisposing factors (chronic reflux, obesity) and a precancerous lesion (specialized intestinal metaplasia of the distal esophagus, the so-called Barrett esophagus) have been defined for esophageal adenocarcinoma.[3] Endoscopic surveillance programs in patients with known Barrett esophagus have been established in many centers. Although the cost–benefit aspects of such surveillance programs are still discussed controversially,[4] they have resulted in a marked increase of esophageal adenocarcinoma diagnosed at early and curable stages.[5–7] Although at many centers, radical esophagectomy and extended lymphadenectomy are still considered the treatment of choice for early esophageal adenocarcinoma, less invasive and organ-preserving surgical and endoscopic approaches are increasingly promoted and used.[8–11] An indiscriminate use of these new technologies may, however, compromise cure and long-term survival, particularly if lymph node metastases are present.[12]

Surprisingly little information is available about lymphatic spread of early adenocarcinoma. Most reported series are small, do not specifically focus on early disease, or do not adequately differentiate adenocarcinoma of the distal esophagus from squamous cell esophageal cancer and adenocarcinoma of the cardia or proximal stomach.[13–18] This is in contrast to numerous large reports on prevalence and pattern of lymphatic spread of early squamous cell esophageal cancer, predominantly originating from Japan.[19–25] Despite the fact that etiology, pathogenesis, tumor location within the esophagus, and characteristics of the affected patients differ substantially between esophageal adenocarcinoma and squamous cell cancer, much of the current practice in treating

early esophageal adenocarcinoma is inferred from the reported Japanese experience with early squamous cell cancer.

We assessed prevalence and pattern of lymphatic spread in patients with early squamous cell and adenocarcinoma in a large single-center case series from the West and evaluated prognostic factors after surgical resection and systematic lymphadenectomy.

MATERIALS AND METHODS

Patient Population

The study population consisted of 290 consecutive patients with early esophageal squamous cell or adenocarcinoma who had a primary surgical resection and systematic lymphadenectomy at the Department of Surgery of the Technische Universität München over a 15-year period (1990–2004). This series constitutes 19.9% of all prospectively documented resections for esophageal cancer performed in this institution at the specified time period.

Early esophageal cancer was defined, based on the final histopathologic report of the resection specimen, as tumor limited to the mucosa or submucosa and not extending into the muscular wall of the esophagus. This definition also included patients who had resection for high-grade dysplasia (HGD), now termed intraepithelial neoplasia (HGIEN).[26]

To obtain homogenous study populations, patients with early adenocarcinoma of the gastric cardia or proximal stomach invading the distal esophagus were carefully excluded.[27] Also excluded were all patients who had preoperative radiation, chemotherapy, or combined radiochemotherapy and all patients with previous or synchronous malignant tumors. Based on the guidelines for cancer staging of the International Union Against Cancer (UICC),[28] patients with less than 6 removed regional lymph nodes were also excluded to avoid an error in lymph node staging.

Of the 290 study patients, 157 had adenocarcinomas of the distal esophagus and 133 had squamous cell cancer. All but 3 of the early adenocarcinomas were located in the distal esophagus. Of the 133 early squamous cell cancers, 62 (46.6%) were located at or above the level of the tracheal bifurcation and 71 (53.4%) were located in the distal esoph-

agus below the level of the tracheal bifurcation. Demographic parameters of the study population are shown in Table 1.

None of the patients in the study population had evidence of systemic tumor spread on standardized preoperative staging. All patients were considered fit for an extensive surgical procedure based on functional risk evaluation.

Surgical Approach

The used surgical approaches for patients with early squamous cell and adenocarcinoma are listed in Table 1. The standard surgical approach was an abdomino-right-transthoracic en bloc esophagectomy with 2-field lymphadenectomy for squamous cell cancer (110 of 133 patients) and a radical transhiatal tumor resection with extensive lymphadenectomy in the lower posterior mediastinum in patients with adenocarcinoma of the distal esophagus (121 of 157).[29,30] A subgroup of elderly patients with early squamous cell cancer and compromised pulmonary function (n = 23) also had a radical transhiatal approach. In contrast, 36 patients with early adenocarcinoma and enlarged mediastinal nodes on preoperative staging had an abdomino-right-thoracic approach. In 55 of the patients with early adenocarcinoma of the distal esophagus, a transhiatal distal esophageal resection with jejunal interposition was performed,[7] whereas the remainder of the patients with a transhiatal approach had a subtotal esophagectomy and cervical anastomosis.[29]

The extent of lymphadenectomy in the upper abdominal compartment and lower posterior mediastinum was identical for all surgical approaches and comprised a suprapancreatic lymphadenectomy, including all lymph nodes along the common hepatic artery, celiac axis, and splenic artery toward the splenic hilum. The left gastric artery was always transected at its origin and remained with the specimen. Also included were all lymph nodes along the proximal two thirds of the lesser gastric curvature and the gastric fundus, left and right paracardiac nodes, distal paraesophageal nodes, and nodes in the lower posterior mediastinum up to the tracheal bifurcation. With the transhiatal approach, this was achieved after a wide anterior splitting of the diaphragmatic hiatus and transhiatal exposure of the lower posterior mediastinum. Details of this procedure have been described elsewhere.[29,30]

TABLE 1. Demographic Data of Patients With Early Esophageal Cancer in the Study Population Shown According to Histologic Tumor Type

Parameter	Squamous Cell Cancer	Adenocarcinoma	*P*
No. of patients	133	157	
Male:female	4.5:1	9.8:1	<0.01
Median age (range)	58 (36–80)	62 (32–88)	<0.01
Tumor location			
At or above the level of the tracheal bifurcation	62	3	<0.01
Below the level of the tracheal bifurcation	71	154	
Surgical approach/extent of lymphadenectomy			
Abdominothoracic	110	36	
Radical transhiatal	23	121	<0.01
Median number of removed lymph nodes (range)	28 (10–104)	24 (6–58)	<0.01

Patients with an abdomino-right-thoracic approach had an additional formal extended mediastinal lymphadenectomy comprising all nodes at the tracheal bifurcation along the left and right main stem bronchi, the upper mediastinal compartment, and along the left recurrent nerve. A systematic cervical lymphadenectomy was not performed routinely.

Histopathologic Workup

All resection specimens were assessed by a senior pathologist. Specimen analysis was performed in a standardized fashion with prospective documentation of all assessed parameters. Classification of the depth of tumor infiltration was performed according to standard criteria into high-grade intraepithelial neoplasia, carcinoma limited to the mucosa (pT1a category), and carcinoma invading the submucosal layer but not beyond (pT1b category).[26] In patients with multicentric cancers, the tumor with the deepest depth of infiltration or largest diameter was chosen as the main tumor.

All removed lymph nodes were identified according to their location (celiac axis, left gastric artery, lesser gastric curvature, left and right paracardial, paraesophageal distal in the posterior lower mediastinum, bifurcation, and upper mediastinum), counted, and assessed separately.

Standard histopathologic analysis of lymph nodes was performed by serial sections of 5-μm thickness and staining with hematoxylin–eosin and van Gieson. Immunohistochemistry was performed to search for lymph node micrometastases in all patients staged as pN0 on standard histology as described previously.[31]

Lymphatic vessel invasion (also termed lymphangiosis) was defined as tumor cell spread through the lymphatic vessels (ie, carcinoma cells floating within the endothelial-lined space).

Follow Up and Statistical Analysis

Routine follow up was performed by the oncologic outpatient clinic or the patient's general practitioner. For the purpose of this study, the survival status of 277 of 290 (95.5%) patients could be ascertained in February 2005. The median follow up of these patients is 66 months.

All evaluated parameters were prospectively documented throughout the study period in a dedicated database. A 2-tailed Fisher exact test was used to compare proportions. Median and mean values were compared by standard statistical tests as appropriate. All tests were 2-sided; a *P* value of less than 0.05 was considered significant. Survival rates were calculated according to the Kaplan-Meier method and tested with the log-rank test.[32] Postoperative 30-day and hospital mortality were not excluded from this calculation. To assess independent predictors of survival, a Cox multiple regression analysis was performed.[33] Death was chosen as the end point for the multivariate analysis. Tested variables included "histologic tumor type" (adenocarcinoma vs squamous cell carcinoma), "depth of tumor infiltration" (HGIEN/pT1a vs pT1b), "number of removed nodes," "presence of lymph node metastases" (pN0 vs pN+), "surgical approach" (abdomino-thoracic vs radical transhiatal), and "tumor location" (above/at vs below the level of the tracheal bifurcation).

All analyses were performed using the statistical package SPSS for Windows (release 11.0; SPSS Inc, Chicago, IL).

RESULTS

Overall, early esophageal squamous cell cancer accounted for 15% of all resected squamous cell cancer, and early adenocarcinoma accounted for 27% of all resected esophageal adenocarcinomas carcinomas during the study period.

Postoperative mortality in patients with resection for early esophageal cancer was 1.7% (5 of 290). There was no difference in the postoperative mortality between the various surgical approaches and between patients with early squamous cell and adenocarcinoma of the esophagus.

On histopathologic analysis of the resection specimen, early squamous cell cancer was less frequently well differentiated (G1/G2 grading) and had a higher prevalence of associated lymphatic vessel invasion as compared with early adenocarcinoma (Table 2). Of the 157 early adenocarcinomas, 135 (86%) had an intestinal growth pattern. A complete macroscopic and microscopic resection of the primary tumor (R0 resection) was achieved in all patients with early adenocarcinoma. Of the 133 patients with early squamous cell cancer, 2 had microscopic residual tumor at the oral resection margin.

Analysis of the depth of tumor infiltration also showed significant differences between early adenocarcinoma and early squamous cell cancer (Table 2). A submucosal tumor invasion (pT1 category) was present in 107 of 133 (80.5%) patients with early squamous cell cancers as compared with 87 of 157 (55.4%) patients with early adenocarcinoma.

The median number of removed lymph nodes was higher in the 146 patients with an abdominothoracic approach (median, 32; range, 15–104) as compared with the 144 patients with a radical transhiatal approach (median, 23; range, 6–42). There was no significant difference in the lymph node count between patients with radical transhiatal distal esophageal resection and radical transhiatal subtotal esophagectomy. The number of removed nodes was higher in

TABLE 2. Histopathologic Tumor Characteristics in Patients With Early Esophageal Squamous Cell and Adenocarcinoma of the Esophagus

Parameter	Squamous Cell Cancer	Adenocarcinoma	*P*
No. of patients	133	157	
Grading			<0.01
G1/G2	65	116	
G3/G4	68	41	
Lymphatic vessel invasion			<0.01
Absent	99	141	
Present	34	16	
pT category			<0.01
HGIEN	1	13	
pT1a (mucosa)	25	57	
pT1b (submucosa)	107	87	

HGIEN indicates high-grade intraepithelial neoplasia according to Vienna classification.[26]

patients with early squamous cell cancer (median, 28; range, 10–104) as compared with patients with early adenocarcinoma (median, 24; range, 6–58) (Table 1).

None of the patients with high-grade intraepithelial neoplasia had lymph node metastases on routine and immunohistochemical analysis of the removed nodes. This was also the case in the patients with esophageal adenocarcinoma limited to the mucosa, whereas 2 patients with pT1a squamous cell cancer had lymph node micrometastases on immunohistochemical analysis. The overall prevalence of lymphatic spread in tumors limited to the mucosa was not significantly different between squamous cell cancer and adenocarcinoma. Of the 107 patients with squamous cell cancer invading the submucosa, 30 had lymph node metastases on routine assessment of the removed nodes, and an additional 9 patients had micrometastases on immunohistochemical analysis, accounting for an overall 36.4% (39 of 107) prevalence of lymphatic spread in this patient group. In contrast, the overall prevalence of lymphatic spread in patients with submucosal invasion of an esophageal adenocarcinoma was significantly lower ($P = 0.012$). Sixteen of 87 patients had lymphatic spread on routine evaluation of the removed nodes, and an additional 2 patients were found to have micrometastases on immunohistochemical analysis, accounting for an overall prevalence of 20.7% (18 of 87).

The topographic distribution pattern of lymph node metastases differed markedly between patients with squamous cell and adenocarcinoma. Figure 1 shows the number of patients with positive nodes at the specified topographic regions. To account for possible effects of tumor location, the pattern of lymphatic spread in patients with early squamous cell cancer located below the level of the tracheal bifurcation is shown separately from that of patients with early squamous cell cancer located at or above the level of the tracheal bifurcation. In patients with early adenocarcinoma, the predominant site of lymphatic spread was to the locoregional nodes in the lower posterior mediastinum, left and right paracardial region, and along the lesser gastric curvature. Less than 2% of the patients had lymph node metastases in more distant regions, eg, the celiac axis. None of the patients had distant lymphatic spread in the absence of locoregional lymph node metastases. In contrast, lymph node metastases were more widely distributed in patients with early squamous cell cancer. Positive celiac axis nodes were found in 3 of 71 (4.2%) patients with early squamous cell cancer of the distal esophagus. This pattern was even more pronounced in patients with early squamous cell cancer located at/above the level of the tracheal bifurcation. Positive intraabdominal nodes were present in 7 of 62 (11.3%) patients; 5 of these patients had positive nodes at various intraabdominal locations.

On multivariate analysis, the type of surgical approach, tumor location, depth of tumor infiltration, and number of removed nodes had no independent effect on survival. Presence of lymph node metastases and histologic tumor type were the only independent factors for long-term survival. The survival curves for these 2 parameters are shown in Figures 2 and 3. The 5-year survival rate was 79.5% for patients without lymph node metastases versus 48.2% for patients with lymphatic spread, and 83.4% for early adenocarcinoma versus 62.9% for early squamous cell cancer. Compared with squamous cell cancer, the prognostic advantage of tumor type "adenocarcinoma" was also present when only patients with pN0 category, only patients with mucosal cancer, and only patients with submucosal cancer were compared.

DISCUSSION

Current controversies regarding the treatment of early esophageal cancer focus primarily around the adequacy of local endoscopic therapy, the need for lymph node dissection,
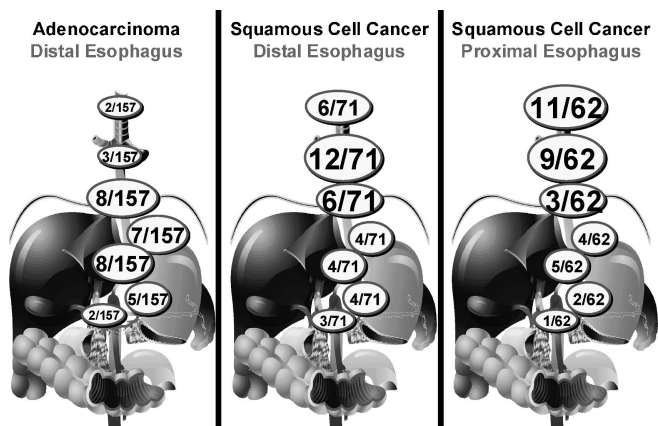

FIGURE 1. Topographic distribution of lymph node metastases shown as the number of patients with positive nodes at the specified regions in relation to the total number of patients in the group. (**A**) Patients with early adenocarcinoma (all but 2 located below the level of the tracheal bifurcation). (**B**) Early esophageal squamous cell cancer located below the level of the tracheal bifurcation. (**C**) Early esophageal squamous cell cancer located at or above the level of the tracheal bifurcation. In patients with lymph node metastases at more than one location, all locations are shown.
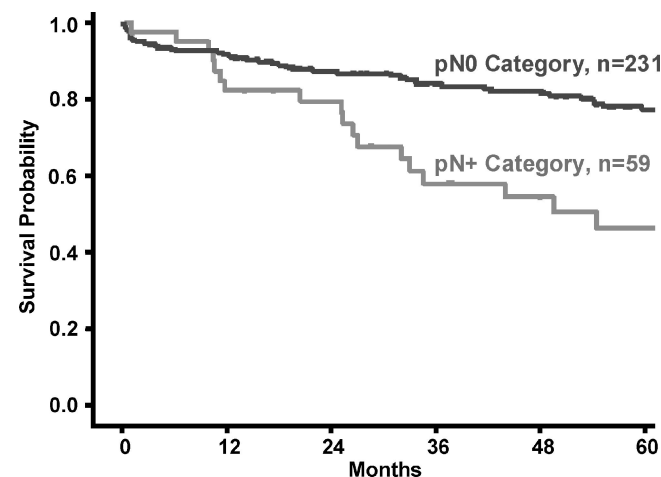

FIGURE 2. Overall survival rate of resected early esophageal cancer in relation to the presence of lymph node metastases (pN0 vs pN+) ($P < 0.01$).
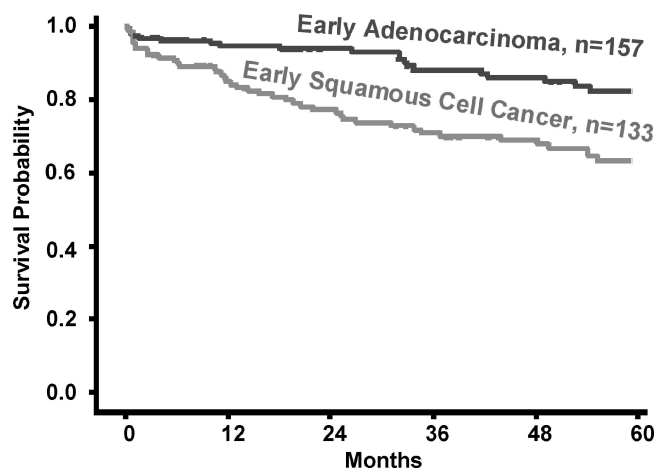
FIGURE 3. Overall survival rate of resected early esophageal cancer in relation to histologic tumor type (adenocarcinoma vs squamous cell cancer) ($P < 0.01$).

and the required extent of lymphadenectomy to achieve a complete clearance of all potentially involved lymph nodes. Although pattern of lymphatic spread, indications for lymphadenectomy, and extent of lymph node dissection for early esophageal squamous cell cancer have been well defined in large series from Japan, very little such data are available on early esophageal cancer seen in the Western world. The present analysis shows that early esophageal adenocarcinoma is the predominating entity among early esophageal cancers in the West. Prevalence and pattern of lymphatic spread as well as the prognosis after surgical resection differed markedly between early adenocarcinoma and squamous cell cancer. Different treatment strategies may thus be applicable to early esophageal squamous cell and adenocarcinoma.

The prevalence and pattern of lymphatic spread in early esophageal squamous cell cancer in the present study matches that reported in large Japanese series.[19–24] Lymph node metastases may already be present in up to 10% of patients with mucosal cancer and up to 50% of patients with submucosal invasion. In the Japanese experience, a subdivision of the mucosal and submucosal layer into m1, m2, m3, sm1, sm2, sm3 categories provides further discrimination. According to these data, lymphatic spread only occurs after infiltration of the m3 layer with a marked rise in the prevalence of lymph node metastases from the sm1 to the sm3 categories. Only patients with m1 and m2 categories thus appear good candidates for endoscopic therapy without lymphadenectomy.[23,24] In the West, however, virtually no patient presents with m1 or m2 mucosal squamous cell cancer. This is also reflected in the present series. Surgical resection with lymphadenectomy will thus remain the major pillar of therapy for patients with early squamous cell cancer in the Western world.

In contrast, referrals for early esophageal adenocarcinoma are increasing rapidly in the West. This is clearly related to endoscopic surveillance in patients with Barrett esophagus, the single most important precursor lesion of esophageal adenocarcinoma. This is also reflected in the present study with an increasing number of such patients

during the past 15 years, and a relative high proportion of high-grade intraepithelial neoplasia and cancer limited to the mucosa among these. Lymph node metastases were found in none of the patients with high-grade intraepithelial neoplasia or adenocarcinoma limited to the mucosa, whereas prevalence of lymphatic spread in patients with submucosal adenocarcinoma was substantially lower as compared with submucosal squamous cell cancer. This may be the result of the less aggressive extent of mediastinal lymphadenectomy used in patients with distal adenocarcinoma and missing potentially involved lymph nodes. However, the 5-year survival rate of 89% in pN0 patients with early esophageal adenocarcinoma, which was significantly higher than the corresponding survival rate in patients with pN0 early squamous cell cancer, argues against this contention.

In the published literature, the prevalence rate of lymph node metastases in patients with submucosal esophageal adenocarcinoma ranges from 13% to 44%.[13–18] However, most of these series are small and inhomogeneous in that they usually also include early adenocarcinomas of the gastric cardia and subcardiac cancers. In the 2 largest of these published series by Buskens et al[16] and Rice et al,[17] the respective prevalence rates were 28% and 19%. These numbers are in concert with the prevalence rate of 21% observed in the present series.

The extent of lymphadenectomy required to achieve complete clearance of all potentially involved nodes is discussed controversially. Based on recent studies, which showed lymph node metastases in the upper mediastinum and cervical region in up to 30% of patients with early distal and proximal esophageal cancer, some recommend an extended 3-field lymphadenectomy in all patients with early tumors irrespective of location and histologic tumor type.[34,35] This rather high rate of lymphatic spread to the neck in early cancers cannot be corroborated or refused by the present study, because the majority of patients had no formal lymphadenectomy in these regions. However, the present study shows that, at least in patients with early distal adenocarcinoma, skipping of lymph nodes stations is extremely rare. In fact, none of the patients with early adenocarcinoma had positive distant nodes without numerous locoregional lymph node metastases. In our opinion, lymphatic spread to distant sites in concert with multiple positive regional nodes must be considered an indicator of systemic disease, which cannot be cured by extended lymphadenectomy.[36] With some restrictions, this is also true for early squamous cell esophageal cancer located in the distal esophagus. In contrast, upper mediastinal and cervical lymph node metastases in patients with proximal early squamous cell cancer constitute locoregional lymphatic spread.[21,22] The potential benefits of extended upper mediastinal and cervical lymphadenectomy in this situation must be weighed against the added morbidity of this procedure.

The present study shows substantial differences in the prevalence and pattern of lymphatic spread between early esophageal adenocarcinoma and squamous cell cancer. This may at least in part be explained by differences in tumor location and depth of invasion into the mucosa or submucosa.

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However, even after accounting for these factors, lymphatic spread in early adenocarcinoma started at a later state of tumor penetration into the esophageal wall and followed a more regular pattern. More than 85% of all positive nodes in early adenocarcinoma were located in close anatomic proximity to the primary tumor in contrast to less than 60% in patients with early squamous cell cancer. This phenomenon may be related to differences in the etiology and pathogenesis of these tumor entities. While smoking and alcohol abuse are the major risk factors for squamous cell cancer in the Western world, esophageal adenocarcinoma results from a chronic and repetitive inflammatory insult to the esophageal mucosa as a consequence of severe and longlasting gastroesophageal reflux with repetitive bouts of esophagitis and the development of intestinal metaplasia.[3,37] This may lead to occlusion of superficial lymphatic channels and thus hamper early tumor cell spread along the usually extensive submucosal lymphatic network of the esophagus. This hypothesis is supported by the observation that lymphatic vessel invasion was significantly less common in patients with early esophageal adenocarcinoma as compared with early squamous cell cancer. Previous reports indicating that lymphatic vessel invasion is an independent prognostic factor in patients with squamous cell esophageal cancer but not esophageal adenocarcinoma also support this concept.[38,39]

In addition to the presence of lymph node metastases, the tumor type (adenocarcinoma vs squamous cell cancer) was also identified as an independent prognostic factor in patients with early esophageal cancer. Patients with early adenocarcinoma had a significantly better prognosis than patients with early squamous cell cancer, irrespective of the depth of tumor infiltration or the presence of lymph node metastases. This is in concert with a previously reported analysis of our entire population with resected esophageal cancer,[40] which showed a significant survival advantage of adenocarcinoma as compared with squamous cell cancer. The present study confirms this finding in the subgroup of patients with early disease. A similar observation was recently reported by Mariette et al,[41] whereas others could not confirm a prognostic difference between esophageal adenocarcinoma and squamous cell cancer.[34,35] The latter, however, usually included cardia and subcardiac cancers in the adenocarcinoma group. Adenocarcinoma of the gastric cardia and subcardiac gastric cancers are known to have a worse prognosis compared with distal esophageal adenocarcinoma.[42]

The reason why histologic tumor type should constitute a prognostic factor in early esophageal cancer independent of the presence of submucosal invasion or lymphatic spread is unclear. Compared with squamous cell cancer, adenocarcinoma was associated with a series of additional favorable parameters, eg, more favorable tumor cell differentiation (grading), a favorable growth pattern (Lauren classification), and a lesser degree of lymphatic vessel invasion. Although none of these individual parameters reached statistical significance as a prognostic factor when assessed alone, their combination may have contributed to the better prognosis of adenocarcinoma. Another possible explanation for the worse prognosis of squamous cell cancer may be related to the type of affected patients: patients with squamous cell cancer usually have more severe comorbid conditions, a worse nutritional and functional status, and a lower social status.[43] In fact, a large proportion of patients with esophageal squamous cell cancer will develop second primary cancers, mostly again in the upper aerodigestive tract, and succumb to these rather than to recurrences from squamous cell cancer.[44] Histologic tumor type "adenocarcinoma" may thus just constitute a surrogate parameter for a combination of more favorable patient and tumor characteristics.

Taken together, the present study shows that, in contrast to early squamous cell cancer, lymphatic spread starts later, is less prevalent, and usually restricted to locoregional nodes in early esophageal adenocarcinoma. Most patients with early adenocarcinoma thus do not require radical esophagectomy and extensive lymphadenectomy. Limited forms of surgical resection appear to suffice.[7,12] Theoretically, endoscopic therapy constitutes an even more attractive alternative to surgical resection in patients with high-grade intraepithelial neoplasia and adenocarcinoma limited to the mucosa, because none of these patients had lymphatic spread in the present analysis. However, several factors argue against a wide spread and uncritical application of endoscopic treatment modalities in these patients. First, the presence of submucosal invasion can currently not be assessed with sufficient accuracy by noninvasive staging techniques. Even with the use of modern high-resolution endoscopy and ultrasonography, approximately half of the patients with subsequent histologically proven submucosal tumor infiltration were wrongly classified as mucosal cancer in a recent study from an expert center.[45] Second, patients with early adenocarcinoma frequently have multicentric neoplasia within the underlying Barrett mucosa.[6,7] This may easily be missed without a complete resection specimen.[6,7] Third, in the largest reported series as yet on endoscopic mucosectomy for early esophageal adenocarcinoma a complete tumor removal was possible in only 75% of patients; in more than half of these patients, this required 2 or more sessions, ie, tumor removal occurred in fractions.[46] Finally, current endoscopic resection and ablation techniques usually do not allow complete removal of the entire segment with intestinal metaplasia, which constitutes the precursor lesion for esophageal adenocarcinoma. Rather, islets of glandular precancerous and often dysplastic Barrett epithelium usually persist on the mucosal surface or beneath squamous cell reepithelialization and provide the ground for new tumors.[12] These factors explain the unacceptably high rate of tumor recurrences and metachronous tumors of 30% and more after alleged curative removal of early esophageal adenocarcinoma by endoscopic techniques.[10] Endoscopic therapy for early esophageal adenocarcinoma can currently not be considered standard and should not be used outside of clinical studies.

Rather, the focus should be guided toward accurate pretherapeutic identification of patients with and without lymph node metastases. Several technologies have been assessed to achieve this goal. Positron emission tomography has so far not met the promise of accurate lymph node staging in esophageal cancer. Despite some enthusiastic reports in the

literature, endoscopic ultrasound with fine needle aspiration of lymph nodes has also been disappointing in daily practice. More promising is the concept of using endoscopic mucosal resection as a staging modality to identify true mucosal cancers, which will not need lymphadenectomy.[47] In the future, prediction of lymphatic spread may also be possible based on molecular parameters of the primary tumor and the use of artificial neural networks.[48,49] Most attractive for current practice is, however, the application of the sentinel node concept. A number of preliminary reports from several centers has shown that identification of sentinel nodes and reliable prediction of the lymph node status based on histopathologic and immunohistochemical evaluation of the sentinel nodes may be possible.[50–52] If this holds true, lymphadenectomy with its associated morbidity could be safely omitted in most patients with early esophageal cancer without compromising cure rates.

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Discussions

DR. TOM R. DEMEESTER (LOS ANGELES, CALIFORNIA): The issue in this presentation focuses on the well-recognized principle that the 2 pillars on which the therapy of solid cancers depends are early recognition and complete removal. In comparison to these 2 pillars, all other therapies pale in their ability to cure.

Now, these principles have led to a problem. The problem is that the surgical therapy of early cancer is resisted by the patient's fear of surgery, and that is particularly so if the operation is an esophagectomy. This fear has given rise to new technology to treat early tumors by less invasive means, such as mucosal ablation and endoscopic mucosal resection. The concern is that these new techniques may compromise complete removal. The work presented by Dr. Stein is very important in its application by providing insight to determine when the extent of surgical extirpation can be reduced safely without compromising outcome.

Dr. Stein's take home message is that the number of early adenocarcinomas is increasing. This is something unique in the history of esophageal cancer. He has reported that the early squamous cell carcinomas are more apt to extend into the submucosa and have lymphatic spread than the early adenocarcinomas. To draw these conclusions he has not only studied patients with tumors confined to the mucosa,

but has also included patients with tumors that extend into the submucosa. The inclusion of the latter may confuse the issue.

A question I have for you, Dr. Stein, is that none of your 70 patients with intramucosal adenocarcinomas had positive nodes whereas 2 of 26 intramucosal squamous cell carcinomas had involved nodes. Are those 2 groups statistically different? Is there a statistical difference between these 2 groups to support the concept that very early intramucosal squamous cell tumors are more aggressive?

The second question is: Are you sure that the surgical procedure performed by your unit did not affect your results? You did a transthoracic and transabdominal en bloc resection for squamous cell carcinomas, that is through both the chest and abdomen, and a modified radical transhiatal resection for most of your adenocarcinomas. We have learned with our transthoracic and transabdominal en bloc resection for intramucosal adenocarcinoma that there is a 6% incidence of positive nodes. This leads me to be suspect that maybe your unit did not get a large enough sample of nodes.

Further, when I analyze our surgical outcome for adenocarcinoma that extended into the submucosa, all of whom had an en bloc procedures, we find that 31% have positive nodes, and when we do a transhiatal, 15% have positive nodes. You reported 21% with your modified radical procedure done through the transhiatal route. This is in the middle between our 31% and 15%. This also calls into question whether the resection done by your unit for adenocarcinoma was adequate enough to be able to make a statement about the extent of lymph node metastasis in early intramucosal adenocarcinoma.

My last 2 questions are relatively brief. First, did any of your intramucosal adenocarcinomas develop systemic disease, indicating that an intramucosal adenocarcinoma can be a lethal disease? The last question is: should surveillance, which you so nicely show is able to pick up early tumors, be encouraged when others advise us not to do so because it has not been shown to be cost effective?

DR. HUBERT J. STEIN (MUNICH, GERMANY): Was the prevalence of lymphatic spread different between mucosal squamous cell cancer and mucosal adenocarcinoma? We had 2 out of 26 in the first group and 0 out of 70 in the second group. This was on statistical analysis not significant, but still it is an 8% versus 0% incidence. We never found a lymph node metastasis in the bigger group of 70 patients with early mucosal adenocarcinoma cancer. I think that this is the major message.

The second question is more difficult to answer: Was our surgical approach to adenocarcinoma, which was mostly through a radical transhiatal approach, adequate enough to really find all lymph node metastasis? I have 3 comments to make. The first: we do have a rather equivalent number of removed lymph nodes with our radical transhiatal approach as compared to the abdomino-thoracic approach? The second

comment is that one obviously can have a higher lymph node count if you remove more nodes in the upper mediastinum. We never found lymph node metasteses in the upper mediastinum in the absence of local regional positive nodes. The third comment to this question is, if we really had missed a substantial number of lymph node metastases with our transhiatal approach in patients with adenocarcinoma, we would expect a worse survival rate and a higher recurrence rate in these patients with early adenocarcinoma. But in fact we had a better survival rate with a less aggressive surgical approach in patients with adenocarcinoma as compared to a significantly lower survival rate in patients with squamous cell cancer, who really had a more radical surgical approach.

To your third question, regarding recurrences in patients with mucosal cancer: yes, we have seen such patients. One of the patients with a mucosal adenocarcinoma died due to systemic recurrences, not local recurrences. So I agree that this is a lethal disease.

Your last question, do I believe in surveillance even though the cost-benefit data do not really support this? Of course I do believe in surveillance. Virtually all the patients that we now see with early stage disease, which are curable by surgical resection, are coming from surveillance programs.

DR. CARLOS A. PELLEGRINI (SEATTLE, WASHINGTON): I wanted to take on this last issue that you just responded to Dr. DeMeester. I am prompted to get up because I heard him say surveillance model, and you say you do believe in surveillance. So let me ask you, with regard to surveillance, what do you do with a patient in whom you find high grade dysplasia? You resected, if I read the numbers right, 13 patients with high grade dysplasia. Do you always recommend surgical resection? Would you do anything different, like an endoscopic mucosal resection or recommend something different?

A second part of the same issue is, could you tell us how many patients did you have preoperative diagnosis of high grade dysplasia in this group of patients under surveillance whose diagnosis was changed once you removed the entire specimen?

And the last question is: Now that you have answered the questions presented at the beginning how should one treat an adenocarcinoma at the T1A level? Do you think a radical transhiatal esophagectomy is necessary? Does it make a difference to remove the nodes either from a prognostic factor—or would you say that a transhiatal esophagectomy should be enough?

DR. HUBERT J. STEIN (MUNICH, GERMANY): In fact there were 13 patients with Barrett esophagus and high-grade dysplasia in this series. None of those patients did have lymph node metastasis.

What is our recommendation today for high grade dysplasia? I think the data are getting more and more solid if you do have confirmed high-grade dysplasia. But this is a difficult thing to confirm even for an experienced pathologist. If it is a very short segment of Barrett esophagus with high-grade dysplasia confirmed by a second expert pathologist, I think this patient could have, without compromising his chances for cure, an endoscopic mucosal resection. If the specimen of the endoscopic mucosal resection confirms high-grade dysplasia, the patient is, to all likelihood, cured because his chances to have lymph node metastasis in all published series.

Did we have patients where the prediagnosis was high-grade dysplasia and after resection it was changed to mucosal or submucosal cancer? Yes, we do have a number of these patients. Actually in the series I presented, a substantial portion had only high-grade dysplasia diagnosed before surgery and we went ahead and did an esophagectomy. I think it was about 25 of those patients with high-grade dysplasia diagnosed before surgery and only 13 of those patients ended up to have actual high-grade dysplasia. That means 12 of those patients had more advanced disease, ie, mucosal or submucosal carcinoma. This is why resection is absolutely required for high-grade dysplasia. Whether it is a surgical resection or an endoscopic mucosal resection which gives you a specimen that you can analyze histopathologically, does not make much difference, in my opinion. If the pathological report comes back and it is not high-grade dysplasia, but invasive carcinoma, then you have to go back and do a formal resection.

What is our formal recommendation today for mucosal adenocarcinoma? We never found lymph node metastasis in these patients. I therefore believe that these patients do not need lymphadenectomy. The problem is to predict that it is really mucosal cancer on the basis of your preoperative testing that you have available, eg, endoscopy and high resolution endoscopic ultrasonography. Today it is not possible with sufficient accuracy to predict mucosal cancer. So these patients again will either need a diagnostic mucosectomy to confirm that it is in effect mucosal cancer or these patients will need a straightforward limited surgical resection. They will probably not need, based on our data, an extended lymphadenectomy.

DR. JACK A. ROTH (HOUSTON, TEXAS): The lower survival of the T1B squamous patients is unexpected. So I would ask you what the pattern of recurrence is for these patients. Is it primarily local regional or is it metastatic? Are you now recommending these patients go on induction chemoradiation protocols because of the relatively lower survival that you see?

DR. HUBERT J. STEIN (MUNICH, GERMANY): This has also been intriguing to us, why would squamous cell cancer have a worse survival. We looked at the recurrence pattern, and most of the recurrences that we see are systemic and not local regional. So there appears to be an earlier systemic dissemination in squamous cell cancer.

Secondly, patients with squamous cell carcinoma often develop second cancers because of the underlying predisposing factors, smoking and alcohol abuse. In fact, 10 patients who had submucosal squamous cell cancer completely resected, developed second cancers, (mostly lung cancers) and they died from these second cancers. We did not see this in patients with adenocarcinoma.

Dr. Harold J. Wanebo (Providence, Rhode Island): In reference to your designation of T1A versus T1B for the adenocarcinomas, it appears you have gone to the use of the sentinel lymph node technique for staging the patient. I wonder if you could explain this procedure? Is this a thoracoscopic approach? Because it sounds like you are doing this preoperatively, prior to resection. Or do you do this along with your resection?

Dr. Hubert J. Stein (Munich, Germany): This is a study in progress, and I have shown you only preliminary data which indicate that the concept may be working in the future. Sentinel node removal is right now still done immediately before resection. We are not drawing any therapeutic conclusions right now, we are collecting data. All patients are still undergoing systematic lymphadenectomy.